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(54) Title: **PHARMACEUTICAL AND COSMETIC COMPOSITIONS AGAINST SKIN AGING**

(57) Abstract: Pharmaceutical and cosmetic compositions for the prevention of skin aging, containing phospholipid complexes of extracts of *Vitis vinifera*, and phospholipid complexes of standardized extract from *Centella asiatica*.

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PHARMACEUTICAL AND COSMETIC COMPOSITIONS AGAINST SKIN AGING

The present invention relates to pharmaceutical and cosmetic compositions against the skin aging containing ingredients of vegetable origin.

More particularly, the present invention relates to pharmaceutical and
5 cosmetic compositions for the prevention of skin aging, containing phospholipid complexes of extracts of *Vitis vinifera*, and phospholipid complexes of triterpenes extracted from *Centella asiatica*.

Skin aging is a complex biological process affecting various layers of the skin, but whose major effects are seen in the dermis. There are two
10 biologically independent aging processes that occur simultaneously. The first is intrinsic aging, which affects skin as well as, most likely, the internal organs. The second is extrinsic aging or photo-aging which is the result of exposure to the elements, primarily ultraviolet irradiation. The consequences of innate aging can be observed all over the skin, including
15 areas protected from the sun. In the areas exposed to the sun, particularly the face and the backs of the hands, photoaging damage is superimposed to tissue degeneration due to innate aging. Thus, the most noticeable changes on facial and neck skin, the primary areas that patients are concerned about, result from the combination of intrinsic and extrinsic aging processes. It has
20 been suggested that as much as 80% of facial aging may be ascribed to exposure to the sun, although other factors (i.e. cigarette smoking) can contribute to premature wrinkling.

From a biochemical standpoint, photoaging is thought to be induced mainly by: some proteases, mainly metalloproteases, which are
25 overproduced and overreleased by keratinocytes and fibroblasts as a

consequence of the interaction with ultraviolet radiation (these proteases are degradative enzymes irreversibly damaging collagen, elastin and hyaluronic acid, bringing about dermis scars and visible wrinkles); and by oxidative stress, able to eliminate the normal skin antioxidant defenses in a very short
5 time.

On the basis of these general considerations, it is clear the need to protect the skin from premature aging by a tool able to counteract the action of the proteases on the dermis (while increasing the capability of fibroblasts to produce and release new collagen fibers) and the disappearance of the
10 antioxidant defenses from the skin.

The present invention fulfills this need, by providing pharmaceutical and cosmetic compositions containing the following ingredients of vegetable origin:

- a) phospholipid complexes of standardized extract 0.1 – 2.5%
15 of *Vitis vinifera*,
- b) phospholipid complexes of standardized extract 0.1 - 2.5%
of *Centella asiatica*.

More preferably, the pharmaceutical and cosmetic compositions of the present invention contain the following ingredients of vegetable origin in
20 the following percentages:

- a) phospholipid complexes of standardized extract 1%
of *Vitis vinifera*,
- b) phospholipid complexes of standardized extract 1%
of *Centella asiatica*.

25 The phospholipid complexes of standardized extract of *Vitis vinifera* (also referred to as "components a") are disclosed in EP 275,224. Said extracts consist of the polyphenolic fraction contained in *Vitis vinifera* seeds, and comprise gallic acid, monomers, dimers, trimers, tetramers,

pentamers, examers and heptameters of catechin and epicatechin free and esterified with gallic acid.

In vitro and *in vivo* studies have evidenced the high antioxidizing activity of said extracts (10 to 200 times as much that of vitamin E, depending on the experimental model), which includes the scavenging of the most reactive radical species, and counteracts all the phenomena related to the activity of free radicals. Said extract is further characterized by the capability to inhibit xanthine-oxidase and to chelate Cu^{++} and Fe^{+++} , thus preventing the enzymatic release of free radicals in tissues. Finally, the extract of *Vitis vinifera* inhibits collagenase and other proteases, thereby protecting the connective tissue and the skin from the harmful action of proteolytic enzymes released following UV irradiation and during the development of an inflammatory skin response, and it has selective affinity to the skin and the circulatory structures, such as microvessels and capillaries, thereby also protecting the microcirculatory district.

The phospholipid complexes of standardized extract of *Centella asiatica* (also referred to as "components b") are disclosed in EP 283,713.

This extract consists of a 4:3:3 mixture of three different molecules having strong activity on collagen metabolism: asiaticoside, asiatic acid and madecassic acid. These molecules improve the capability of the fibroblasts to up-take amino acids such as L-Proline and L-Hydroxyproline that, from a quali-quantitative standpoint, are the most important amino acids in the collagen formula. An improved synthesis of collagen means a faster substitution of the degraded old fibers of collagen with the new ones.

Components a) and b), when tested toxicologically, showed neither toxic nor irritative actions towards the treated tissues.

The compositions of the present invention may optionally contain, in addition to components a) and b) indicated above, also other active

ingredients such as vitamin E (0.2-1%), zinc (0.1-0.3%), hydroxyacids (0.1-1%) and glycyrrhetic acid or a complex thereof with phospholipids (0.1-2.5%), to improve the antioxidant, anti-aging and antinflammatory properties of the composition.

5 The compositions of the present invention will be administered topically, in the form of suitable formulations liquid (such as gel, lotions, milks, emulsions, foams and the like) or solid or semi-solid (such as creams, ointments, lipsticks, and the like). Said formulations will be prepared according to conventional methods, such as those described in "Remington's
10 Pharmaceutical Handbook", Mack Publishing Co., NY, USA, together with suitable excipients, such as emollients, moisturizers, thickening agents, emulsifiers, dyes, flavors and the like.

Some examples of compositions according to the invention are reported in the following.

15 **Example 1 – OIL-IN-WATER EMULSION**

100 g contain:

| | | |
|----|---|--------|
| | Phospholipid complexes of extract of <i>Vitis vinifera</i> | 0.20 g |
| | Phospholipid complexes of triterpenes extracted from <i>Centella asiatica</i> | 1.00 g |
| 20 | Isostearyl isostearate (Gattefossé) | 2.50 g |
| | Polyisoprene (Syntesqual - Vevy) | 2.50 g |
| | Decyl oleate (Cetiol V - Henkel) | 2.00 g |
| | Cetyl palmitate (Cutina CP - Henkel) | 2.00 g |
| | Cetearyl Isononanoate (Cetiol SN - Henkel) | 2.00 g |
| 25 | Polysorbate 80 (Tween 80 -ICI) | 1.00 g |
| | Imidazolidinyl urea | 0.30 g |
| | Tocoferol | 0.20 g |
| | Ascorbyl Palmitate | 0.10 g |

| | | |
|---|---|---------|
| | Methyl chloroisothiazolinone (e) | |
| | Methyl isothiazolinone (Kathon CG-Rohm & Haas) | 0.05 g |
| | Disodium EDTA | 0.10 g |
| | Butylated hydroxytoluene | 0.05 g |
| 5 | Polyacrylamide (e) C ₁₃₋₁₄ Isoparaffin (e) | |
| | Laureth-7 (Spiegel 305 - Seppic) | 2.50 g |
| | Perfume | 0.10 g |
| | Purified water q.s. to | 100.0 g |

Example 2 – OIL-IN-WATER EMULSION

| | | |
|----|---|--------|
| 10 | 100 g contain: | |
| | Phospholipid complexes of extract of <i>Vitis vinifera</i> | 0.50 g |
| | Phospholipid complexes of triterpenes extracted from <i>Centella asiatica</i> | 0.50 g |
| | Phospholipid complexes of glycyrrhetic acid | 1.50 g |
| 15 | C ₁₂₋₁₅ Alkyl benzoate (Finsolv TN - Finetex) | 4.00 g |
| | Cetyl palmitate (Cutina CP - Henkel) | 3.00 g |
| | Polyisoprene (Syntesqual - Vevy) | 2.50 g |
| | Isostearyl isostearate (Gattefossé) | 2.50 g |
| | Polysorbate 80 (Tween 80 -ICI) | 1.00 g |
| 20 | Imidazolidinyl urea | 0.30 g |
| | Methyl chloroisothiazolinone (e) | |
| | Methyl isothiazolinone (Kathon CG-Rohm & Haas) | 0.05 g |
| | Tocoferol | 0.20 g |
| | Ascorbyl Palmitate | 0.10 g |
| 25 | Disodium EDTA | 0.10 g |
| | Citric acid | 0.05 g |
| | Polyacrylamide (e) C ₁₃₋₁₄ Isoparaffin (e) | |
| | Laureth-7 (Spiegel 305 - Seppic) | 2.00 g |

| | |
|--------------------------|---------|
| Butylated hydroxytoluene | 0.05 g |
| Perfume | 0.10 g |
| Purified water q.s. to | 100.0 g |

CLAIMS

1. Pharmaceutical and cosmetic compositions containing the following ingredients of vegetable origin:

- 5 a) phospholipid complexes of standardized extract 0.1 – 2.5%
of *Vitis vinifera*,
b) phospholipid complexes of standardized extract 0.1 - 2.5%
of *Centella asiatica*,

in combination with conventional excipients and carriers.

10 2. Pharmaceutical and cosmetic compositions as claimed in claim 1, containing the following ingredients of vegetable origin:

- a) phospholipid complexes of standardized extract 1%
of *Vitis vinifera*,
b) phospholipid complexes of standardized extract 1%
15 from *Centella asiatica*,

in combination with conventional excipients and carriers.

3. Pharmaceutical and cosmetic compositions as claimed in claim 1 and 2, further containing additional active ingredients selected from the group consisting of vitamin E, zinc, hydroxyacids and glycyrrhetic acid or a
20 complex thereof with phospholipids.

4. Pharmaceutical and cosmetic compositions as claimed in claim 3, wherein the additional active ingredients are present in the following percentages:

- vitamin E 0.2-1%,
25 zinc 0.1-0.3%,
hydroxyacids 0.1-1%,
glycyrrhetic acid or a complex thereof with phospholipids 0.1-2.5%.

5. The use of:

- a) phospholipid complexes of standardized extract of *Vitis vinifera*, and
- b) phospholipid complexes of standardized extract of *Centella asiatica*, for the preparation of pharmaceutical and cosmetic compositions against skin aging.

5 6. The use of:

- a) phospholipid complexes of standardized extract of *Vitis vinifera*, and
- b) phospholipid complexes of standardized extract of *Centella asiatica*, in combination with additional active ingredients selected from the group consisting of vitamin E, zinc, hydroxyacids and glycyrrhetic acid or a
10 complex thereof with phospholipids,
for the preparation of pharmaceutical and cosmetic compositions against skin aging.

7. The use of the cosmetic compositions as claimed in any one of the above claims, against skin aging.

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